The Changing Roles and Targets for Animal Models of Schizophrenia

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Unlike disorders of other fields of medicine (eg., diabetes, heart disease), schizophrenia has been only marginally impacted by the study of animal models. This gap reflects the incomplete understanding of the causes and mechanisms of schizophrenia and the resulting lack of defined targets for model development. However, prior attempts at modeling in animals the complex symptoms of schizophrenia have given way to more promising component models. This review will address the evolving field of animal models of schizophrenia with a focus on models of errors in neurotransmission, and of psychophysiological deficits, with a concluding discussion of the present and future promise of genetic-based models. Evolving models based on the long-held conceptualization of schizophrenia as being based on errors in neurotransmission are discussed as regards the integration of newer findings implicating alterations in dopamine, glutamate and neurotensin function in the pathophysiology and pharmacotherapy of schizophrenia. The case for the more recent conceptualization of schizophrenia as a core deficit in information processing and stimulus filtering is discussed. Animal behavioral paradigms that model psychophysiologic constructs of stimulus processing deficits related to schizophrenia include prepulse inhibition (PPI), a model of sensorimotor gating, or latent inhibition (LI), a model of salience learning. These models represent both better supported associations with schizophrenia and more productive targets and are providing important new information regarding the psychopharmacology of schizophrenia. Genetic models of schizophrenia are based on the demonstrated heritability of the disorder and more recent pharmacogenetic findings for antipsychotic medications. Genetic-based animal models use behavioral or molecular genetic techniques to manipulate behaviors related to schizophrenia by altering the frequencies of related genes. The future development of increasingly informative animal models of schizophrenia will be dependent on a more complete understanding of schizophrenia, an integration of findings across animal models and refinements in the criteria used to assess model "validity" that better reflect the changing nature and roles of animal models of schizophrenia. Biol Psychiatry 2001;50:845–855

Introduction

Schizophrenia is a chronic and ubiquitous illness that afflicts approximately 1% of the world's population. Individuals with schizophrenia represent by far the greatest consumers of mental healthcare services, highlighting the personal and economic hardships associated with this diagnosis. The syndrome of schizophrenia is often characterized by a classical clinical manifestation of psychotic symptoms such as delusions and hallucinations. It is, however, increasingly appreciated that schizophrenia is associated with impairments in many domains of cognitive function that impart disorders of thought and emotion and result in a marked deterioration in social, personal, and occupational functioning (Andreasen 1995). This widespread impairment in critical levels of human functioning underlies the devastating nature of this diagnosis and the complexity and diversity of its clinical phenotype.

Additional clinical features of schizophrenia related to this discussion include its time course and gender-dependent presentation. Clinical symptoms of schizophrenia typically first appear between 15 and 25 years of age in men, whereas women typically exhibit an age of onset about five years later than men (Szymanski et al 1995). Perceptible impairments in motor or cognitive functions may, however, appear earlier in life. Other than age of onset, additional gender differences include a generally more severe course of illness, more pronounced brain abnormalities, and a greater refractoriness to treatment in male than in female patients (Cowell et al 1996; Nopoulos et al 1997; Szymanski et al 1995). An additional relevant clinical feature of schizophrenia is that despite recent incremental improvements, the pharmacotherapy of schizophrenia remains characterized by incomplete benefits offset by clear risks for adverse events.

Advances in medical research have elucidated the etiology and pathophysiology of major medical disorders such as hypertension and diabetes. These advances have lead to life-saving advances in their diagnosis and treatment. Leading the way in these investigations has been the

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development and study of animal models of these disorders. In contrast, the causes and mechanisms of schizophrenia remain poorly understood and little informed by animal models. Despite being a long-standing focus of psychiatric researchers, animal models have made relatively little impact on the diagnosis and treatment of schizophrenia. No diagnostic procedures or major new medication advances have resulted from decades of study of animal models of schizophrenia. The promise of animal models universally lies in there being simpler, more accessible forms of complex inaccessible human phenomena. With this definition comes an understanding of the perhaps predictable failure of animal models to significantly inform the complex, largely subjective states of schizophrenia. Schizophrenia is a disorder of the highest of human brain functions such as perception and cognition. The truest fact regarding the cause of schizophrenia is that it results from heterogeneous etiologies involving complex interactions among genetic and environmental factors. The pathophysiology of schizophrenia undoubtedly represents a corresponding complexity of abnormalities in multiple brain functions. These properties of schizophrenia present perhaps unique challenges to attempts to develop valid animal models.

A critical question for the future of animal models of schizophrenia is whether such models can direct rather than follow clinical research discoveries. The long history of animal model development in schizophrenia research has followed the latter approach in attempting to develop models of etiologic factors, models that reproduce symptoms of schizophrenia, or models that predict its pharmacology. Previously, the attainment of these goals has been thwarted by the lack of clinically defined targets for model development. Attempts to reproduce in animals its cardinal symptoms of hallucinations, delusions, and thought disorder are predictably futile. A clinical phenotype of schizophrenia is increasingly recognized for its heterogeneous and individually varying properties, and it therefore becomes increasingly difficult to define what exactly constitutes "schizophrenia-like" in developing an animal model. Perhaps the greatest claim of existing animal models is their ability to predict the efficacy, and particularly adverse side effects, of antipsychotic drugs. The evolution of animal models of schizophrenia has progressed from the development of analogous behavioral models of schizophrenia stressing their predictive pharmacology, to the later development of models aspiring to a homologous relationship between the animal behavior and the behavioral effects of schizophrenia, the underlying processes that define schizophrenia, or both.

The future development of animal models of clear relationship to schizophrenia will be dependent on the integration of the rapidly proliferating research findings related to the psychophysiologic, neurodevelopmental, and genetic bases of schizophrenia. Important new developments in elucidating the genetic determinism of schizophrenia, its course over the life cycle of affected individuals and unaffected first-degree relatives, and its psychophysiologic manifestations have provided important new targets for the development of valid animal models of a subtotal description of schizophrenia. It is hoped that these efforts will result in new animal models of schizophrenia that will lead clinical investigation and represent the necessary shift away from the idea of developing an isomorphic model of the syndrome of schizophrenia in animals.

This discussion focuses initially on a selective review of animal behavioral models based on errors in neurotransmission, starting with dopamine-based models and the more recent evolution of glutamate- and neurotensin-based models. Subsequent discussion focuses on current animal models of psychophysiologic constructs of schizophrenia, and finally the present and future roles of genetic models of schizophrenia are elaborated. A concluding discussion will highlight the challenges to be addressed in developing and validating new models. The goal of this work is to use illustrative examples to link past efforts and future directions to define guidelines for the development of increasingly valid animal models to investigate schizophrenia. This effort is not intended as a review of animal models of schizophrenia. A description and critical discussion of extant animal models of schizophrenia can be found elsewhere (Kilts 2001).

Animal Models of Schizophrenia Based on Errors in Neurotransmission

Dopamine-Based Models

Alterations in many classical neurotransmitters and neuropeptides have been implicated in the pathophysiology and pharmacotherapy of schizophrenia. The following discussion focuses on only three of these—dopamine, glutamate, and neurotensin—and is admittedly incomplete in that other implicated neurotransmitters or neuromodulators such as serotonin, glycine, substance P, or cholecystokinin are not covered. The intent of this discussion is to use illustrative examples of this type of model rather than weigh their relative validity.

The origin of dopamine-based models of schizophrenia lies largely in the pharmacologic demonstration of the attenuation and exacerbation of symptoms with dopamine antagonists and agonists, respectively. The culmination of these studies in the dopamine hypothesis of schizophrenia posited that psychotic symptoms of this disorder are due to a hyperdopaminergic brain state (Snyder 1972). The greatest support for this hypothesis was the classic demonstration of

correlation between the in vitro affinity of neuroleptics for the D_2 dopamine receptor and their potency for the treatment of schizophrenia reflected in their average daily dose. As a result, early dopamine-based animal models focused on behaviors related to dopamine receptor antagonists (e.g., catalepsy) and dopamine receptor agonists (e.g., amphetamine-induced stereotypes). Such models were developed with regard only to predictive validity; drug responses observed in the animal bore little or no relationship to the symptoms of schizophrenia. Paradigms such as the inhibition of conditioned avoidance responding in a shuttle box or pole climbing apparatus (Arnt 1982; Kuribara and Tadokoro 1981) or induction of catalepsy (Sandberg et al 1988) were demonstrated to be reliably affected by acute neuroleptic administration. The obvious shortcomings of these and related paradigms were their inability to investigate the mechanisms of schizophrenia and, as they are based on the behavioral responses to older neuroleptic or typical agents, they have a highly limited ability to identify newer atypical antipsychotics that are less mechanistically bound to dopamine receptor antagonism.

To possibly realize their potential, dopamine-based models of schizophrenia must evolve with the increasing understanding of the anatomic and functional complexities of the forebrain dopamine systems and of a pathophysiology of dopamine neurons associated with schizophrenia. An extension of the dopamine hypothesis of schizophrenia posits a hypofunctional state for dopamine neurons innervating the prefrontal cortex to be involved in the negative symptoms and cognitive impairments associated with schizophrenia (Davis et al 1991; Goldstein and Deutch 1992). A cognitive construct model of working memory deficits associated with schizophrenia has incorporated a prefrontal cortical dopamine deficit in rats and monkeys. Subchronic, but not acute, phencyclidine (PCP) administration resulted in impaired performance on a retrieval/detour working memory task (Jentsch et al 1997). The dopamine-based nature of this model was also established. Subchronic PCP administration was associated with neurochemical evidence of a persistent reduction in dopamine neurotransmission in the frontal cortex (Jentsch et al 1999); the degree of reduction in estimated frontal cortical dopamine activity was positively correlated with the level of impaired performance on the retrieval/detour task (Jentsch and Roth 1999). Furthermore, short-term clozapine administration significantly improved working memory in PCP-treated monkeys, yet impaired task performance in control monkeys (Jentsch et al 1997; Jentsch and Roth 1999). This nonhuman primate model thus links cognitive and dopamine system models of schizophrenia and provides preliminary evidence of predictive validity. The relationship between prefrontal cognitive function and its dopaminergic innervation may, however, be complex because function is apparently impaired by both a deficit and excess of dopaminergic input (Arnsten et al 1998). A diminished ability of prefrontal dopamine neurons to maintain their modulatory responses to challenges (e.g., stressors) within a physiologic "window" could potentially impair prefrontal cortical function. A further revision of a prefrontal dopamine deficit model of schizophrenia may thus include a disrupted homeostatic model of regulation of prefrontal function by its dopaminergic innervation.

Future iterations of the involvement of dopamine in neuropathologic models of schizophrenia will have to incorporate the increasing probability that, if dopamine abnormalities are related to schizophrenia, they may be more restricted that previously considered. A recent immunocytochemical study of the postmortem prefrontal cortex in schizophrenic subjects (Akil et al 1999) demonstrated a specific alteration of the dopaminergic innervation of layer 6 of the dorsomedial prefrontal cortex (Brodmann area 9). A further revision of the prefrontal dopamine deficit model of cognitive impairments related to schizophrenia could be based on the effects on spatial working memory or related tasks of prefrontal area- and lamina-specific decreases/increases in dopamine input to the monkey cortex. Although it has been argued that dopamine-based models of schizophrenia have largely exhausted their potential to inform this disorder (Lipska and Weinberger 2000), their incorporation of more restricted anatomic and functional perturbations may yet reinforce this classic model of the neuropathology of schizophrenia.

Glutamate-Based Models

The inability of dopaminergic abnormalities to explain a neuropathology of schizophrenia has led to the search for other errors in neurotransmission and the development of associated models. The psychotomimetic effects of noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonists such as PCP and ketamine in healthy humans (Krystal et al 1994; Malhotra et al 1996) and their ability to exacerbate several psychotic symptoms in schizophrenic patients (Lahti et al 1995a, 1995b; Malhotra et al 1997) have prompted a view of schizophrenia as being related to a hypofunctional state of glutamatergic neurotransmission. Attempts to mimic these effects in animals has lead to the recognition of parallels with behavioral and cellular abnormalities associated with schizophrenia (Table 1). Furthermore, the behavioral effects of subanesthetic doses of phencyclidine or ketamine in rats and monkeys have been shown to be antagonized by the administration of neuroleptic or atypical antipsychotics. Recently, a genetically engineered mouse line ($Nr1^{neo}$ -/-) expressing 5% to 10% of the density of frontal cortical NMDA receptors was shown to exhibit increased motor

Table 1. Parallels between the Behavioral and Cellular Effects of Schizophrenia and of Pharmacologically Induced Decreases in NMDA Receptor Function in Animals

Schizophrenia features	Animal findings
Psychomotor agitation	Increased locomotor activity
Spatial working memory deficits (Park and Holzman 1992)	Spatial working memory deficits
Stereotyped behavior	Stereotyped behavior
Sensorimotor gating deficits (PPI)	Sensorimotor gating deficits (PPI)
Decreased social behavior	Decreased social behavior
Decreased GAD_{67} (Qin et al 1994)	Decreased GAD_{67} (Qin et al 1994)
Reduced prefrontal cortical dopamine release	Reduced prefrontal cortical dopamine release (Jentsch 1999)

NMDA, N-methyl-D-aspartate; PPI, prepulse inhibition.

activity and stereotyped behaviors, and decreased social behavior, compared with wild type mice (Mohn et al 1999). The behavioral effects of the NMDA receptor knockdown were attenuated by the administration of clozapine or haloperidol. Although many of the effects of the NMDA receptor antagonists have been linked to secondary effects on dopamine neurotransmission, the behavioral alterations associated with the $Nr1^{neo}$ -/- mouse line were not associated with alterations in striatal dopamine release. Thus, pharmacologic or genetic models of NMDA receptor hypofunction have significant potential as animal models of the pathophysiology of schizophrenia and as tools in the identification of mechanistically novel antipsychotic drugs.

Neurotensin-Based Models

Although several of the large class of neuropeptide neurotransmitters have been implicated in the pathophysiology and pharmacotherapy of schizophrenia, it is for the tetradecapeptide neurotensin that the most compelling evidence has accumulated (Binder et al, this volume). Human postmortem and cerebrospinal fluid studies support an alteration of neurotensin neurotransmission for at least a subgroup of patients with schizophrenia. The central administration of neurotensin produces in rodents a constellation of behavioral, physiologic, and biochemical effects similar to the systemic administration of antipsychotic drugs (Nemeroff 1980). Antipsychotic drug administration is in turn associated with changes in brain regional neurotensin peptide concentration (Kilts et al 1988), peptide and receptor mRNA (Kinkead et al 2000), and release (Radke et al 1998). Collectively, these data support an association between alterations in neurotensin neurotransmission and the pathophysiology and pharmacotherapy of schizophrenia. Specifically, the neurotensin model of schizophrenia is based on a pathophysiology of diminished neurotensin neurotransmission and an enhanced neurotensin neurotransmission as a final common pathway for the mechanism of action of antipsychotic drugs.

The central administration of neurotensin decreases active avoidance behavior in a conditioned avoidance response (CAR) paradigm (Luttinger et al 1982), an older generation animal model of schizophrenia (Weiss and Kilts 1998). The recent availability of selective, high-affinity neurotensin receptor antagonists (Gully et al 1997) has allowed the assessment of a role of neurotensin in the newer generation animal models of schizophrenia. The prepulse inhibition of startle (PPI) and latent inhibition (LI) paradigms aspire to model the information processing functions degraded by schizophrenia (see below). For PPI, a refinement of the model has been the use of isolation rearing, or the administration of PCP or amphetamine, to mimic deficits in PPI associated with schizophrenia. Rearing or drug-induced deficits in PPI are attenuated by the administration of neuroleptic or atypical antipsychotic drugs (Swerdlow et al 1994, 1996). Pretreatment with the neurotensin receptor antagonist SR 142948A antagonized the haloperidol- or quetiapine-induced restoration of PPI in isolation-reared rats (Binder et al 2001a). Pretreatment with SR 142948A also inhibited the acquisition of LI and antagonized the facilitatory effect of haloperidol administration on LI (Binder et al 2001b). These findings support a role for neurotensin neurotransmission in the sensory inhibition functions degraded by schizophrenia and in the effects of antipsychotic drugs on deficits in sensory inhibition. Because such defects have been proposed to represent core dysfunctions related to the syndromal symptoms of schizophrenia (Swerdlow et al 1994), the case for the potential therapeutic efficacy of a centrally acting neurotensin receptor agonist is supported. As a mechanistic model of schizophrenia, neurotensin-based approaches have considerable promise, although further model testing (e.g., human studies) is clearly necessary.

Models built on the contention of errors in neurotransmission have certain heuristic value yet become better linked to distributed neural system theories of brain function and schizophrenia when they are expanded into neural circuit models. The integration of neuropathologic findings has resulted in arguably better informed models of schizophrenia featuring defects in intracortical (Benes 1998) or subcortical-cortical (Lewis 2000) neural circuits. The further evolution of animal models of clear relationship to schizophrenia will evaluate the behavioral effects of alterations in the interactions between multiple neurotransmitter systems in testing neural processing models.

Psychophysiologic Construct Models

Currently, the most studied animal models of schizophrenia focus on psychophysiologic constructs of deficits in

sensory processing that manifest as stimulus filtering and attentional impairments. Two related paradigms, PPI of a startle response and LI of learned associations, have been studied as homologous models of sensory inhibition processes that are impaired by schizophrenia (Kilts 2001).

Prepulse Inhibition (PPI)

Prepulse inhibition represents an index of sensorimotor gating mechanisms essential to the protection of the integrity of sensory and cognitive information (Swerdlow et al 2000). In all versions, PPI refers to the inhibitory influence of a weak sensory stimulus on the reaction to a startling acoustic or tactile stimulus. In animals, PPI typically is measured as the inhibition of the motor startle response to a loud (~120 dB) acoustic startle stimulus by a preceding (100 msec) weak (5–15 dB above background) prepulse stimulus. In humans, PPI is similarly assessed by the prepulse inhibition of an eye-blink reflex, and the underlying processes are linked to a larger clinical research literature describing the sensory gating of the electroencephalographic evoked potential (P50) that occurs with short latency (50 msec) following an auditory stimulus. Impairments in PPI or P50 gating are observed in patients with schizophrenia (Braff and Geyer 1990; Braff et al 1992) or schizotypal personality disorder (Cadenhead et al 2000a, 2000b). The relationship between PPI and event related potential (ERP) models, however, remain to be established. Deficits in PPI are proposed to reflect the loss of critical processes of sensory inhibition that manifests as sensory flooding of affected individuals and result in cognitive fragmentation. Although deficits in PPI associated with schizophrenia correlate with cognitive and behavioral symptoms (Braff et al 1999), such deficits are apparently not sensitive to antipsychotic medication (Braff and Geyer 1990) nor specific to schizophrenia (Swerdlow et al 1994).

The collective human findings support the contention that an animal behavioral model based on deficits in PPI would have face and construct validity in studying the pathophysiology of schizophrenia (Swerdlow et al 1994; Swerdlow and Geyer 1998). The means of disrupting PPI and their differing effects on antipsychotic drug response models merit discussion. The administration of D_2, but not D_1, dopamine receptor agonists inhibits PPI, although D_1 receptor agonists do potentiate the disruptive effects of D_2 receptor activation on PPI (Peng et al 1990). The selective activation of dopamine receptors in the nucleus accumbens (Swerdlow et al 1990, 1991) or their antagonism in the medial prefrontal cortex (Ellenbroek et al 1996) inhibits PPI of the startle reflex. Nonpharmacologic manipulations also produce reliable and longer-lived disruption of PPI. Neurodevelopmental models of schizophrenia (Lipska and Weinberger 2000) stress the role of disruptions in early brain development in the pathogenesis of schizophrenia. These models are based on evidence of disrupted neurogenesis, history of early stress, and neonatal brain damage in patients with schizophrenia. Perinatal manipulations that interfere with neurogenesis and synaptogenesis result in deficits in PPI (Black et al 1999; Lipska and Weinberger 2000). Early life stressors such as maternal separation or early social isolation result in deficits in PPI in most (Geyer et al 1993; Wilkinson et al 1994; Ellenbroek et al 1998), but not all (Lehman et al 2000), studies in rats. Finally, neonatal damage of the rat ventral hippocampus results in a developmentally delayed emergence of deficits in PPI (Lipska and Weinberger 1995) and an increased sensitivity to the disruptive effects of apomorphine on PPI (Swerdlow et al 1995). Although PPI has demonstrable hereditability (Bullock et al 1997), the disruptive effect on PPI of neurodevelopmental and pharmacological manipulations are also influenced by genetic factors. Comparison of dopamine agonist effects on PPI between rat strains and substrains indicate robust genetic influences on the dopaminergic regulation of sensorimotor gating (Kinney et al 1999; Swerdlow et al 2000). The demonstration of deficits in PPI in unaffected relatives of patients with schizophrenia (Cadenhead et al 2000b) suggests that such deficits represent a genetically transmitted vulnerability factor. These data are consistent with the view of schizophrenia as the result of the interaction of genetic and developmental anomalies. Models based on disrupted PPI therefore have the potential to use the investigative power of animal models to define the neural substrates of this interaction and uniquely inform the pathogenesis and pathophysiology of schizophrenia.

Animal models based on disrupted PPI also have demonstrated potential to inform the neural correlates of the pharmacotherapy of schizophrenia. Antipsychotic drugs antagonize decreases in PPI of the startle reflex produced by apomorphine (Swerdlow and Geyer 1993; Swerdlow et al 1991, 1994) or isolation rearing (Geyer et al 1993; Ellenbroek et al 1998). The disruptive effects of PCP on PPI are opposed by the administration of atypical (Figure 1; Bakshi and Geyer 1995; Swerdlow et al 1996), but not typical (Swerdlow et al 1996), antipsychotic drugs; however, Pietraszek and Ossowaska (1998) reported that PCP-induced deficits in PPI were attenuated by long-term (6 weeks or 3 months), but not short-term (4 days), haloperidol administration in rats. This finding suggests a wider applicability of PCP–PPI animal models to the study of schizophrenia, although this model seemingly remains more informative to the study of the distinct mechanisms of atypical antipsychotics. Collectively, these observations support the use of animal models based on deficits in PPI to explore both the distinct processes underlying the differences between typical and atypical antipsychotics in the treatment of schizophrenia and the adaptive mechanisms thought to underlie the delayed therapeutic response to antipsychotic medications.

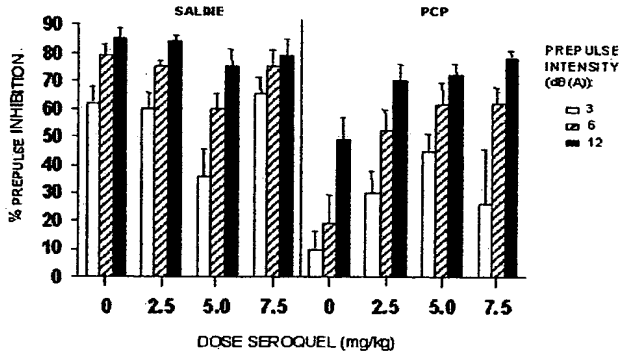

Figure 1. The antipsychotic, seroquel, reverses PCP-induced disruptions in PPI in rats.

Latent Inhibition (LI)

Latent inhibition refers to the inhibition of conditioned associations to a stimulus by prior noncontingent exposures to the stimulus. Thus, LI represents the interaction of nonassociative and associative learning for a stimulus and assesses the ability to accurately categorize a stimulus under conditions of changing salience. As an animal model of a psychophysiologic construct of schizophrenia (impaired sensory inhibition), the phenomenon of LI ascribes to the modeling of attentional processes that are degraded by schizophrenia and result in the use of inefficient and inflexible processing strategies to filter stimuli. In addition, LI claims model validity with constructs of schizophrenia such as deficits in the control of behavior by context (Lubow 1989; Servan-Schreiber et al 1996) and the influence of prior experience on the perception of current events (Hemsley 1987). Comparison of LI in humans and rodents is complicated by the fact that, in humans, LI is typically assessed using paradigms that differ from those used in animals in the incorporation of masking stimuli. With this distinction, the results of most human studies support predictions of disrupted LI associated with schizophrenia. Baruch et al (1988a) demonstrated that LI of a learned stimulus association by stimulus preexposure was absent in patients with acute schizophrenia; control subjects without schizophrenia and a group of subjects with chronic schizophrenia exhibited clear LI. These results led to the proposal that LI paradigms represent a model of the positive symptoms and causal mechanisms (i.e., hyperdopaminergic states) of acute, but not chronic, schizophrenia (Baruch et al 1988a). Subsequent studies indicated that acutely ill schizophrenics (Gray et al 1995; Guterman et al 1996; but see Swerdlow et al 1996) and schizotypal individuals (Baruch et al 1988b; De la Casa et al 1993) exhibit significantly impaired performance compared with normal subjects in an LI paradigm. Thus, LI tasks fulfill elements of face and construct validity as an animal behavioral model of specific attentional processes impaired in schizophrenia. It remains unclear, however, whether disrupted LI reflects a corollary of early illness stages and is reinstated with illness progression (Gray et al 1995) or the disruptive effects of initial antipsychotic medication (Williams et al 1998).

Prepulse and latent inhibition represent nonlearning- and learning-based models of schizophrenia that derive their model validity from their relationship to the key psychophysiologic construct of deficits in sensory stimulus processing; abstract however, unlike PPI, LI is not disrupted by early maternal or social isolation (Ellenbroek et al 1998; Lehman et al 1998; Wilkinson et al 1994) or PCP administration (Christison et al 1991; Weiner and Feldon 1992), and the two paradigms are differentially affected by systemically or intracerebrally administered dopamine receptor agonists (Ellenbroek et al 1996; Killcross and Robbins 1993; Swerdlow et al 1990, 1991). Although conceptually linked, these models are distinct in the functional processes assessed, their neural substrates and modulatory influences such that they are not mutually informative of this disorder.

A major goal of newer animal models related to schizophrenia is the ability to distinguish the effects of typical and newer generation (i.e., "atypical") antipsychotic drugs, with members of both classes "active" in the model. The LI paradigms do have the ability to distinguish the effects of typical and atypical antipsychotics, although the effects of atypical antipsychotics on baseline LI are more controversial and dependent on paradigm variations (Kilts 2001). An essential extension of a LI-based animal model of schizophrenia is the development of disrupted LI to enhance the face and construct validity of the model. The seeming insensitivity of LI to PCP administration or maternal/social isolation precludes its link to important animal models of schizophrenia based on errors in glutamate neurotransmission or neurodevelopmental insults. Consistent with dopamine-based models of schizophrenia, LI in rats is disrupted by amphetamine administration (Killcross et al 1994; Solomon et al 1981; Weiner et al 1984). It has been consistently demonstrated that antipsychotic drug administration reverses the disruption of LI by the acute administration of the indirect dopamine agonist amphetamine; however, there remains a clear need to extend the disrupted LI model beyond the effects of dopamine receptor agonist administration. Genetic models of disrupted LI hold considerable promise because enduring LI deficits could be generated by the use of forward or reverse genetic approaches. The following discussion develops and expands this approach.

Genetic-Based Models

The rapidly emerging understanding of the genetics of complex behaviors has furnished an important future for animal models focusing on both the genetic and neurobi-

ological determinants of schizophrenia. The identification and validation of candidate susceptibility genes that confer vulnerability for schizophrenia will rely on the use of "reverse" genetic approaches in mouse models (Tarantino and Bucan 2000). Genetic linkage analyses have identified chromosomal regions harboring possible susceptibility loci for schizophrenia (Blouin et al 1998; Brzustowicz et al 2000; Schwab et al 1998; Straub et al 1995). The functional analysis of mutations in candidate genes within these regions in mouse genetic models will be critical to the elucidation of the genetic basis of schizophrenia. Similarly, the behavioral analysis of targeted gene mutations also can inform the neurotransmitter mechanisms of schizophrenia. For example, a recent comparison of dopamine D_2, D_3, and D_3 knockout mice (Ralph et al 1999) demonstrated the involvement of the D_2, but not D_3 or D_4 receptor in PPI. In addition to probing the genetic and neurotransmitter determinants of schizophrenia, genetics will also play a role in the development of animal models of schizophrenia in the generation by "forward" genetic strategies of schizophrenia-related behavioral phenotypes. Such an approach begins with a phenotype related to schizophrenia (e.g., PPI, LI) and explores the use of alterations in gene frequency to alter the presence, frequency, or intensity of the behavior to more closely approximate behavioral deficits associated with schizophrenia. Although this approach also has the potential to identify novel schizophrenia-related human genes (Tarantino and Bucan 2000), the potential to develop enduring behavioral disorders linked to schizophrenia that are amenable to pharmacologic, neurobiological, and developmental investigation is enormous. Increasing numbers of strategies have evolved to manipulate gene frequencies and associated behaviors.

GENE KNOCKOUT STRATEGIES. Recent development of behavioral mutants using targeted mutations in gene knockout strategies has demonstrated the ability to uniquely identify the functional significance of the targeted gene and its encoded protein (Usiello et al 2000). Although the majority of derived behavioral mutants are linked to mouse models of anxiety or learning and memory (Tarantino and Bucan 2000), several affected behavioral phenotypes are relevant to animal models of schizophrenia. *Prodh* -/- mice lacking the gene that encodes proline dehydrogenase demonstrate decreased PPI relative to wild-type controls (Gogos et al 1999). Further testing of this candidate genetic model would assess the impact of *Prodh* deletion on related behavioral paradigms such as LI and social interaction, hippocampal neuropathology, and the response to perinatal stressors, and would describe the effects of antipsychotic drug administration on the genetically derived PPI deficits. The further evolution of this knockout strategy involves the use of conditional mutants exhibiting a temporally and anatomically restricted gene mutation (Sauer 1998) to probe the developmentally delayed and neuropathologic features of schizophrenia. Similar to their role in the identification of the *Clock* gene as critical to circadian regulation (Vitaterna et al 1994), random mutagenesis screens using schizophrenia-related phenotypes may also yield behavioral mutants representing candidate animal models of schizophrenia. The targeted overexpression of genes using viral vector technology represents a related and powerful counterpart to knockout strategies.

SELECTION STRATEGIES. Additional and long-standing strategies to manipulate behavioral phenotypes by altering gene frequencies include the use of inbred rodent strains or selective breeding. More than 100 inbred mouse and rat strains are available. Members of a highly inbred strain are genetically identical, and the comparison of inbred strains for schizophrenia-related behavioral phenotypes can potentially identify strains or substrains that exhibit behavioral deficits linked to schizophrenia. This strategy has demonstrated significant strain differences in PPI (Logue et al 1997; Varty et al 1994) and its dopaminergic regulation (Kinney et al 1999; Swerdlow et al 2000; Varty et al 1994). Selective breeding for phenotypic extremes attempts to increase toward homozygosity the frequency of alleles for genes affecting the selected trait while the allelic frequency of trait-irrelevant genes is unaffected. Artificial selection-based models are time-consuming and laborious but have the potential advantage over inbred strain-based models in that only the trait-relevant alleles are targeted. Behavioral selection for enhanced apomorphine susceptibility resulted in a selected rat line (APO-SUS) that also exhibited diminished PPI and LI relative to unselected control animals or a line selected for decreased apomorphine susceptibility (APO-UNSUS; Ellenbroek et al 1995, 2000). This pharmacogenetic selection strategy has also been convincingly applied to the development of rodent models of schizophrenia modeling neuroleptic response and nonresponse (for a review, see Kilts 2001).

A word of caution regarding the development of animal behavioral models by genetic manipulations relates to the need for strict control of environmental variables and genetic backgrounds and to the careful phenotyping of animals using batteries of tasks. The recent comparison of eight inbred mouse strains and a 5-HT_{1B} receptor knockout mouse line using six strictly standardized behavioral tests and testing environments in three laboratories demonstrated differing behavioral profiles between sites (Crabbe et al 1999). Differences between inbred mouse strains in the behavioral response to amphetamine admin-

Table 2. Guidelines for the Development of the Next Generation of Animal Models of Schizophrenia

A focus on the development of subtotal (endophenotype) models of schizophrenia
The need to link models to evolving clinical features of schizophrenia
The need to redefine criteria for assessing validity of animal models
Demonstrate a horizontal integration of findings across models
The need to develop reliable behavioral phenotypes to evaluate models

istration were also drastically altered following an ecologically relevant period of restricted access to food (Cabib et al 2000). The genetic background hosting a transgenic or knockout gene manipulation also has a major effect on the behavioral phenotype (Gerlai 1996). These findings highlight the importance of defining and controlling both the interaction between genes and between genes and environment in the use of genetic manipulations to develop animal behavioral models of schizophrenia.

Concluding Comments

Schizophrenia arguably represents the most troublesome of the psychiatric disorders. The mental and social well-being of humans is dependent on the discovery of the causes and mechanisms of schizophrenia and the use of that knowledge to direct the development of new treatments and preventive measures. Animal models can and must have a role in this process. A critical challenge to attaining this role is to define how we can use the power of animal models to manipulate candidate causal factors and invasively explore the consequences of such manipulations; investigative strategies that are highly limited in humans. It would seem that effectively addressing this challenge necessitates additional critical thinking as to the roles and targets of animal models of schizophrenia. Enduring and newer concepts proposed as guidelines for the development of the next generation of animal models of schizophrenia are outlined in Table 2 and discussed below.

The contention that schizophrenia is a uniquely human disorder does not negate the feasibility of developing relevant animal models, but only defines the challenge to and sets the limitations of an animal model. The impossibility of developing animal models that capture the totality of the complex syndrome of schizophrenia now seems obvious. The unfeasibility of reproducing in animals the fully expressed phenotype of schizophrenia argues for a more piecemeal recreation of modelable components or endophenotypes of schizophrenia. Borrowing from genetics, another scientific field dependent on capturing accurate phenotypes, and the move toward subtotal or endophenotype models offers more realistic chances to develop valid animal models of schizophrenia.

It would seem that a needed area of evolution of animal models of schizophrenia, or of psychiatric disorders in general, relates to the redefinition of model validity and how it is assessed. As the intended roles of animal models of schizophrenia evolve, so does the source of their validity and the criteria by which this is assessed. Although model validity continues to refer to the closeness of the association of the model to schizophrenia, the categorization of models as being valid or invalid is not sufficiently described. As the field moves away from holistic models of schizophrenia, a particular model may be valid in one application, whereas it may be invalid in its application to another feature of schizophrenia. For instance, although an induced deficit in PPI in adult rats may have valid relationship to key psychophysiologic impairments related to schizophrenia, it might bear no relationship to the pathogenesis of the disorder. Although several sets of criteria have been proposed for assessing model validity, the most frequently invoked are the criteria associated with predictive, face, and construct validity proposed by Willner (1984). The claim of phenomenlogic or theoretical equivalence that underlie face and construct validity, respectively, represents more the source of the claim of model validity than a benchmark by which proof of validity can be established. This seems ultimately to fall to evidence of predictive validity. Finally, the evaluation of model validity will depend on the development of batteries of tasks to accurately define behavioral phenotypes and the integration of findings across behavioral, developmental, neuropathologic, and pharmacologic investigations.

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